Polygenic risk for hypertriglyceridemia is attenuated in Japanese men with high fitness levels

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DYSLIPIDEMIA, DEFINED AS AN increased level of triglycerides (TG) and LDL cholesterol (LDL-C) or a decreased level of HDL cholesterol (HDL-C), is an important risk factor for coronary heart disease (CHD) (34, 39). The main cause of CHD is atherosclerosis, a condition in which the arterial wall becomes thick and hard as a result of plaque accumulation (15, 18). When too much LDL circulates in the blood, LDL complexes accumulate in the arterial walls, and they are oxidized. Subsequent uptake of oxidized low-density lipoprotein (OxLDL) by macrophages is thought to play a central role in atherosclerotic plaque formation (7). In contrast to LDL-C, HDL-C protects against plaque formation by delivering excess LDL-C from the blood to the liver (2). TG has also been shown to play a central role in atherosclerosis by changing LDL particle size (42), which is associated with LDL-C oxidation (14). Therefore, TG, LDL-C, and HDL-C contribute to the pathogenesis of atherosclerosis and CHD. In fact, longitudinal cohort studies have revealed that they are independently associated with the incidence of CHD (13, 21, 53).

Genetic variation is an important factor in the determination of blood lipid levels. Several twin studies showed that the heritability of blood lipid levels is >50% (4, 5, 24). Moreover, recent genome-wide association studies (GWAS) identified several single nucleotide polymorphisms (SNPs) that are strongly associated with blood lipid levels (3, 58, 60), and these results were replicated in various populations, including Japanese (11, 57). For example, the risk allele for a SNP in the apolipoprotein A-V (APOA5) gene increases blood TG levels by 16.95 mg/dl (58). It has been demonstrated that these SNPs are associated with not only blood lipid levels but also increased susceptibility to CHD (3, 60).

In contrast, considerable evidence indicates that increased physical activity results in higher cardiorespiratory fitness (CRF) and reduced risk for CHD in part by improving the blood lipid profile (12, 33, 50). Because physical activity and CRF are strongly associated with blood lipid levels, it raises the question whether or not physically active individuals can reduce their genetic risk for dyslipidemia. A number of SNPs have been shown to attenuate the beneficial effects of exercise on blood lipid profile (22, 59). Conversely, several studies showed that a high level of physical activity attenuated the genetic risk for dyslipidemia (49, 54). However, these previous studies only focused on a single SNP. Because lipid-associated SNPs were shown to have additive effects on lipid phenotype (31, 37), it is necessary to determine whether high CRF diminishes polygenic risk for dyslipidemia.

In the present study, we calculated three genetic risk scores (GRSs) based on SNPs related to TG, LDL-C, and HDL-C, all of which were identified by large-scale GWASs and were replicated in Japanese populations. We examined the effect of CRF on the relationships between each GRS and blood lipid levels.
profile under the hypothesis that high CRF modifies the polygenic risk associated with high TG and LDL-C or low HDL-C levels.

MATERIALS AND METHODS

Subjects. One hundred seventy Japanese men aged 20–79 yr participated in this study. All subjects had no history of stroke or CHD. We excluded subjects on lipid-lowering medication and those with serum TG levels >400 mg/dl. Diabetes status was defined in accordance with World Health Organization criteria, and 10 subjects (5.9%) had diabetes. Current and former smoking status was assessed with a questionnaire. Daily alcohol and saturated fat intake were assessed in a brief-type self-administered diet history questionnaire (32). Body weight and body fat percentage were measured on an electronic scale (Inner Scan BC-600; Tanita, Tokyo, Japan), and height was measured with a stadiometer (YL-65; YAGAMI, Nagoya, Japan). All subjects provided written informed consent before enrollment in the study. The research project was approved by the Ethical Committee of Waseda University.

CRF. CRF was assessed with a maximal graded exercise test on a cycle ergometer (Ergomedic 828E; Monark, Varberg, Sweden) and quantified as maximal oxygen uptake ($V\dot{O}_2$max). The highest value of $V\dot{O}_2$ recorded during the exercise test was considered the $V\dot{O}_2$max). The graded cycle exercise began at a workload of 45–90 W and was increased by 15 W/min until the subject could no longer maintain the required pedaling frequency of 60 rpm. Heart rate and ratings of perceived exertion were monitored each minute during exercise. During the incremental portion of the exercise test, expired gas was collected from the subjects. $O_2$ and $CO_2$ concentrations were measured and averaged over 30 s intervals by using an automated gas analyzer (Aeromonitor AE-300; Minato Medical Science, Tokyo, Japan). The highest value of $V\dot{O}_2$ recorded during the exercise test was considered the $V\dot{O}_2$max (ml·kg⁻¹·min⁻¹), and achievement of $V\dot{O}_2$max was accepted if at least three of the following four criteria were achieved: the $V\dot{O}_2$ curve showed a plateau despite increasing the work rate, the maximal heart rate was 95% of the age-predicted maximal heart rate [220 – age (in years)], the respiratory exchange ratio was >1.1, and the subject achieved a perceived exertion rating of 18 or greater. Subjects were subsequently divided into low-CRF (low-fitness) and high-CRF (high-fitness) groups according to the reference $V\dot{O}_2$max values from the Japanese population, and 10 subjects were selected into each group (3, 16, 17, 31, 52, 57). All selected SNPs of European descent and replicated in Japanese populations (Table 1), were in Hardy-Weinberg equilibrium ($P_{\text{HWE}} > 0.05$) in the current analysis because it was identified as the strongest genetic factor determining LDL-C levels in a Japanese population (57). $TRIB1$ rs6982636 and $APOA5$ rs662799 were not included in the SNP array in the present study; these were replaced with rs2954029 and rs2266788, which are in complete linkage disequilibrium with $TRIB1$ rs6982636 and $APOA5$ rs662799, respectively ($r^2 = 1.00$, in HapMap JPN). Additionally, $APOA5$ rs964184 was in complete linkage disequilibrium with $APOA5$ rs2266788 in our study population ($r^2 = 1.00$). Therefore, rs964184 was excluded; the remaining 19 SNPs were in Hardy-Weinberg equilibrium ($P > 0.01$), and their MAF was $>0.05$ in this population (Table 1).

Table 1. SNPs selected to calculate GRS

| Phenotype | Gene | SNP | Chromosome | Base Pair Position (GRCh37.p10) | Allele (M|M) | MAF | $\beta$-Coefficient* | HWE P |
|-----------|------|-----|------------|-------------------------------|-------------|-----|----------------------|-------|
| TG        | ANGPTL3 | rs10889353 | 1 | 63118196 | A/C | 0.14 | 0.117 | 0.325 |
|           | GCKR  | rs780094 | 2 | 27741237 | A/G | 0.49 | 0.126 | 0.539 |
|           | AFF1  | rs442177 | 4 | 88030261 | A/C | 0.49 | 0.040 | 0.167 |
|           | MLXIPL | rs17145738 | 7 | 72982874 | A/T | 0.01 | 0.091 | 0.658 |
|           | TRIB1 | rs2954029 | 8 | 126949072 | T/A | 0.49 | 0.117 | 0.658 |
|           | LPL   | rs328† | 8 | 19819724 | C/G | 0.13 | 0.178 | 0.480 |
|           | APOA5 | rs2266788† | 11 | 116660686 | T/C | 0.28 | 0.322 | 0.181 |
| LDL-C     | SORT1 | rs646776 | 1 | 109818530 | A/G | 0.07 | 0.252 | 1.000 |
|           | HMGCR | rs350662 | 5 | 74651084 | C/T | 0.47 | 0.085 | 0.280 |
|           | ABO   | rs507666 | 9 | 136149399 | G/A | 0.28 | 0.098 | 1.000 |
|           | APOE  | rs7412 | 19 | 45412079 | C/T | 0.06 | 0.629 | 1.000 |
|           | APOE  | rs4420638 | 19 | 45422946 | A/G | 0.12 | 0.221 | 0.254 |
| HDL-C     | LPL   | rs328 | 8 | 19819724 | C/G | 0.13 | -0.211 | 0.480 |
|           | ABCA1 | rs4194268 | 9 | 107647220 | G/A | 0.36 | -0.090 | 0.506 |
|           | APOA5 | rs2266788 | 11 | 116660686 | T/C | 0.28 | -0.191 | 0.181 |
|           | LIPC  | rs1800588 | 15 | 58723675 | C/T | 0.50 | -0.158 | 0.542 |
|           | CETP  | rs3764216 | 16 | 56993324 | G/T | 0.22 | -0.254 | 0.654 |
|           | CETP  | rs1532624 | 16 | 57005479 | G/T | 0.33 | -0.187 | 0.730 |
|           | LCAT  | rs255049 | 16 | 68013471 | T/C | 0.12 | -0.056 | 0.290 |
|           | LIPG  | rs4939883 | 18 | 47167214 | C/T | 0.23 | -0.062 | 0.031 |

GRS, genetic risk score; TG, triglyceride; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; M, major allele; m, minor allele; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium. *The values were obtained from Japanese replication study data (50). †The SNPs were also used to calculate HDL-GRS.
SNP genotyping. Nuclear DNA was extracted from peripheral blood using the QIAamp DNA Mini kit (QIAGEN, Hilden, Germany), and DNA quality was evaluated by agarose gel electrophoresis and spectrophotometry. We confirmed that none of the DNA samples were fragmented and that the A260/A280 ratio was 1.8–2.0. SNP genotyping was performed by using the Infinium Human Exome BeadChip version 1.1 (Illumina, San Diego, CA) according to the manufacturer’s protocol. Genotype calling was performed using the GenTrain clustering algorithm (ver. 1.0) in the GenomeStudio (ver. 2011.1, Illumina). Cluster boundaries were determined with the standard cluster files provided by Illumina. The SNP call rate was at least 98.7% for all samples.

**Calculation of GRS.** We calculated three GRSs, one each for TG (TG-GRS), LDL-C (LDL-GRS), and HDL-C (HDL-GRS) based on the 19 selected SNPs. Because LPL rs328 was associated with TG and HDL-C, it was used to calculate both HDL-GRS and TG-GRS. APOA5 rs2266788, which was selected to calculate the TG-GRS, was also shown to be associated with HDL-C levels with a genome-wide significant P value in a Japanese replication study. Therefore, it was included in the calculation for the HDL-GRS. Consequently, the number of SNPs used to calculate the GRSs was seven for TG-GRS, five for LDL-GRS, and nine for HDL-GRS. All the SNPs used to calculate the GRSs are shown in Table 1, and the substituted SNPs (rs6892636 and rs6672799) and excluded SNP (rs964184) were not used to calculate any GRS. We assumed that each SNP acts in an additive manner, and the GRSs were calculated by a weighted method (47, 51). Each SNP was weighted by its relative effect size ($\beta$-coefficient) obtained from previous Japanese replication study data (57). The weighted scores for each SNP were calculated by multiplying each $\beta$-coefficient by the number of corresponding risk alleles. These scores were totaled to obtain a GRS for each subject. Each GRS was adjusted so that the maximum was 100. We divided subjects into the low-, middle-, and high-GRS groups according to the tertile of each GRS for subsequent analysis. The range for each GRS group was as follows: for TG-GRS, low: 24–53, middle: 53–63, high: 64–98; for LDL-GRS, low: 39–72, middle: 73–80, high: 81–96; for HDL-GRS, low: 32–54, middle: 55–65, high: 66–88.

**Statistical analysis.** All statistical analyses were performed with SPSS version 21.0 (SPSS, Chicago, IL) or PLINK version 1.07 (Massachusetts General Hospital, Boston, MA). The allelic frequencies of the selected SNPs were calculated by a gene-counting method, and Hardy-Weinberg equilibrium and linkage disequilibrium for each SNP were assessed by the chi-square test. The values of TG and HDL-C were log transformed due to their nonnormal distribution. One-way ANOVA or ANCOVA adjusted for age was used to evaluate the differences between low- and high-fitness groups. We evaluated the influence of fitness level and GRS group on each lipid parameter by two-way ANCOVA adjusted for appropriate covariates such as age, BMI, percent body fat, TG, ApoB, and current or former smoking. A post hoc test with Bonferroni correction was used to identify significant differences among mean values if a significant main effect or interaction was identified. Fisher’s exact test was used to compare subjects with hypertriglyceridemia (serum TG level $\geq$150 mg/dl) in the TG-GRS groups. All measurements and calculated values are presented as means $\pm$ SD. P values $<0.05$ were considered statistically significant.

**RESULTS**

**Comparison of subject characteristics between low- and high-fitness groups.** The characteristics of the study subjects are shown in Table 2. Age, BMI, percent body fat, TG, ApoB, and current or former smoking were lower in the high-fitness group than in the low-fitness group. The high-fitness group also had higher $\text{VO}_{2\text{max}}$, HDL-C, ApoA-I, and saturated fat intake than the low-fitness group.

**Comparison of serum TG levels among TG-GRS groups and fitness groups.** We next compared the anthropometric characteristics and blood lipid parameters among the TG-GRS groups and the low- and high-fitness groups (Table 3). Anthropometric characteristics (age, height, body weight, BMI, and percent body fat) and $\text{VO}_{2\text{max}}$ were not different among the TG-GRS groups. However, a significant interaction effect between TG-GRS group and fitness group was observed on body weight ($P<0.05$). Body weight was higher in the low-fitness group than in the high-fitness group only in the high TG-GRS group ($P<0.05$). Two-way ANCOVA adjusted for covariates, including age and BMI, detected a significant interaction effect between TG-GRS group and fitness group on serum TG levels (Fig. 1A). Serum TG levels were higher in the high and middle TG-GRS groups than in the low TG-GRS group only in the low-fitness group ($P<0.01$ and $P<0.05$), whereas no significant difference was observed in serum TG levels among the TG-GRS groups in the high-fitness group. Moreover, the number of subjects with hypertriglyceridemia (TG $\geq$150 mg/dl) was higher in the high and middle TG-GRS groups than in the low TG-GRS group only in the low-fitness group ($P<0.05$); however, a significant interaction effect was not observed between TG-GRS group and fitness group on oxLDL.

**Comparison of serum LDL-C levels among LDL-GRS groups and fitness groups.** Anthropometric characteristics and blood lipid parameters were also compared among the LDL-GRS groups and fitness groups (Table 5). Body weight, BMI, and percent body fat were lower in the middle LDL-GRS group than in the low LDL-GRS group. The other anthropometric characteristics and $\text{VO}_{2\text{max}}$ did not differ among the LDL-GRS groups. Serum levels of Total-C and LDL-C were higher in the...
**Table 3. Association of subject characteristics with TG-GRS groups and fitness groups**

<table>
<thead>
<tr>
<th>TG-GRS</th>
<th>Low</th>
<th>Middle</th>
<th>High</th>
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<tbody>
<tr>
<td>Low</td>
<td>23</td>
<td>35</td>
<td>28</td>
</tr>
<tr>
<td>Middle</td>
<td>32</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td>High</td>
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</table>

- **Age, yr**: 63.1 ± 14.1, 65.6 ± 10.9, 59.6 ± 13.8
- **Height, cm**: 167.7 ± 6.9, 167.5 ± 6.7, 170.3 ± 6.9
- **Body weight, kg**: 65.5 ± 8.4, 67.1 ± 11.5, 71.1 ± 8.5
- **BMI, kg/m²**: 23.2 ± 2.2, 23.8 ± 3.2, 24.5 ± 2.1
- **Body fat, %**: 20.4 ± 5.2, 21.0 ± 5.7, 22.4 ± 4.0
- **Total-C, mg/dl**: 206.2 ± 35.4, 211.4 ± 33.8, 216.0 ± 32.9
- **LDL-C, mg/dl**: 120.1 ± 34.1, 124.8 ± 30.6, 127.8 ± 25.5
- **HDL-C, mg/dl**: 61.1 ± 13.7, 56.2 ± 15.6, 55.8 ± 8.4
- **ApoB, mg/dl**: 99.4 ± 25.0, 103.7 ± 22.8, 107.5 ± 18.6
- **ApoA-I, mg/dl**: 149.6 ± 25.4, 142.5 ± 25.5, 145.5 ± 19.1
- **V̇O_{2}\text{max}, ml·kg⁻¹·min⁻¹**: 27.4 ± 4.8, 26.7 ± 4.6, 28.4 ± 4.0
- **Body fat, %**: 20.4 ± 5.2, 21.0 ± 5.7, 22.4 ± 4.0

Data are means ± SD. HDL-C was log transformed for analysis (data are shown as the original values). Data were analyzed by 2-way ANCOVA with adjustment for age, BMI, current or former smoking status, history of diabetes, alcohol consumption, and saturated fat intake as appropriate. *P < 0.05 vs. the low TG-GRS group within the same fitness group. †P < 0.05 vs. the low-TG-GRS group within the same fitness group.

The main findings of this study were that subjects with high CRF overcame their polygenic risk for hypertriglyceridemia. Blood TG levels are complex traits regulated by multiple genes except in the case of monogenic familial hypertriglyceridemia (30). Numerous SNPs associated with blood TG levels have been identified by candidate gene approaches or GWAS and have been repeatedly replicated in various ethnic populations (3, 11, 16, 17, 31, 52, 57, 58, 60). Previous studies have shown that serum TG levels gradually increased as the risk alleles for TG-associated SNPs increase (58). In contrast, the effectiveness of regular exercise on blood lipid profile improvement has been reported in a large number of epidemiological and intervention studies (12, 33, 50). Therefore, it is important to clarify whether high CRF attenuates polygenic risk for hypertriglyceridemia.

Several studies have examined the effects of physical activity or fitness level on the association of TG-related genetic variations and blood TG levels. Sentí et al. (54) reported that the H+H+ genotype of the lipoprotein lipase (LPL) HindIII polymorphism was only associated with increased serum TG levels in physically inactive men who had a smoking habit. Moreover, it was reported that the TG-raising effect of the ApoA-II-265TT genotype was blunted in high-fitness men (49). However, these studies focused on only a single gene, and the effects of physical activity or CRF on the polygenic effects of blood TG levels have never been examined. Therefore, we calculated a TG-GRS based on seven selected SNPs, all of which have been shown to be associated with blood TG levels both by large-scale GWASs in Caucasian populations and by replication in Japanese populations. The mean serum TG level was 25.8 mg/dl higher in subjects in the top tertile than in those in the bottom tertile of TG-GRS, suggesting that the selected SNPs additively increase serum TG levels (data not shown).

Despite the strong polygenic risk for hypertriglyceridemia, serum TG levels were not different between the high and low TG-GRS groups in the high-fitness group (Fig. 1A). These results suggest that high CRF attenuates even the high polygenic risk for hypertriglyceridemia.

It is well known that both acute and chronic exercise decreases blood TG levels, and the underlying mechanism is primarily dependent on the increased activity and expression of LPL, which is the major enzyme responsible for the hydrolysis of TG (23). Some of the seven selected SNPs used to calculate the TG-GRS are located in genes associated with LPL activity. LPL rs328 (p.S447X) is a gain of function variant that generates a truncated LPL protein with increased LPL activity (43). Moreover, angiopoietin-like 3, encoded by ANGPTL3, inhibits LPL activity by enhancing its cleavage (36). Therefore, the difference in serum TG levels among the TG-GRS groups may be explained in part by LPL activity.
the presence of the minor allele for \textit{LPL} rs328 (19). Furthermore, it was also reported that the maximum heritability of exercise training-induced changes in the levels of serum TG and LPL activity was modest (22 and 15\%, respectively) (27). Therefore, a large amount of regular exercise and high CRF may increase LPL activity regardless of genetic background and abolish polygenic risk for hypertriglyceridemia.

In the present study, we divided the subjects into high- and low-fitness groups according to the reference \( \dot{V}O_{\text{2max}} \) values in the prevention of lifestyle-related diseases issued by the Ministry of Health, Labor, and Welfare of Japan. Serum TG level is one of the criteria for metabolic syndrome in Japan (41), and the reference value is 150 mg/dl. In the high and middle TG-GRS groups, 16 subjects with low CRF had serum TG levels \( \geq 150 \) mg/dl, whereas in the high-fitness group, only three subjects had serum TG levels \( \leq 150 \) mg/dl (Table 4). Therefore, our results could be used as evidence supporting the reference values of \( \dot{V}O_{\text{2max}} \) for the prevention of lifestyle-related diseases in Japan.

Recent epidemiological studies have revealed that, in addition to LDL-C and HDL-C, blood TG levels are an independent predictor of CHD (53). Although blood TG does not cause atherosclerotic plaque growth, elevated blood TG increases the small dense LDL particles that are susceptible to oxidation (14, 42); thus, they are thought to play an important role in plaque formation and increase the risk of CHD. Consistent with this

Table 4. Comparison of a number of subjects with hypertriglyceridemia (TG \( \geq 150 \) mg/ml) among TG-GRS groups and fitness groups

<table>
<thead>
<tr>
<th></th>
<th>Low TG-GRS ((n = 86))</th>
<th>High and Middle TG-GRS ((n = 115))</th>
<th>Fisher’s Exact Test</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low fitness</td>
<td>0 (0.0)</td>
<td>16 (25.4)</td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>High fitness</td>
<td>1 (3.1)</td>
<td>3 (5.8)</td>
<td></td>
<td>1.000</td>
</tr>
</tbody>
</table>

Data are the number of subjects with hypertriglyceridemia (%). Boldface indicates significance \( (P < 0.05) \).
molecular mechanism, plasma OxLDL levels were higher in the high TG-GRS group than in the low TG-GRS group (Table 3). We determined whether high CRF suppressed elevation of plasma OxLDL and serum TG even in the high TG-GRS group. However, even in the subjects with high CRF, plasma OxLDL levels were higher in the high TG-GRS group than in the low TG-GRS group. Additional investigations in larger cohorts along with measurements of lipoprotein particle size are required to address this.

Contrary to our hypothesis, high CRF did not modify the polygenic effects on serum LDL-C, HDL-C, and other lipoprotein profiles (i.e., ApoB, ApoA-I, and OxLDL; Fig. 1, B and C, Tables 5 and 6). Several studies have reported that high levels of physical activity or CRF modify the association between various SNPs and blood lipoprotein levels (8, 9). However, because they only focused on a single gene, it was not known whether high CRF diminished the polygenic effects of these SNPs on LDL-C, HDL-C, and other lipoprotein profiles. Our results suggest that the polygenic effects of these SNPs on the serum levels of these lipoproteins remain even in individuals with high CRF. Several twin studies report that the heritability of LDL-C and HDL-C was slightly higher than that of TG (4, 5, 56), indicating that serum LDL-C and HDL-C levels were more affected by genetic factors than are TG.

Differences in the genetic contribution of each SNP toward each lipid phenotype may explain the inconsistent results for CRF-mediated modification of the polygenic effects on blood TG, LDL-C, and HDL-C levels. Nevertheless, our limited sample size might have led to a type 2 error. Our findings should be replicated in a large sample cohort study to conclude whether high CRF can modify the polygenic risk for high LDL-C and low HDL-C levels.

However, in all HDL-GRS groups, the serum levels of HDL-C and ApoA-I in individuals with high CRF were higher than those in individuals with low fitness (Fig. 1C, Table 6). This result suggests that regular exercise and sustained high CRF are recommended to maintain higher levels of HDL-C regardless of genetic predisposition. In addition, although se-

Data are means ± SD. TG and HDL-C were log transformed for analysis (data are shown as the original values). Data were analyzed by 2-way ANCOVA with adjustment for age, BMI, current or former smoking status, history of diabetes, alcohol consumption, and saturated fat intake as appropriate. *P < 0.05 vs. the low LDL-GRS group within the same fitness group. †P < 0.01 vs. the low LDL-GRS group within the same fitness group. Boldface indicates significance (P < 0.05).
Physical activity and maintain a high level of CRF. Concerned with their lipid profiles even though they are genetic risk for elevated blood LDL-C levels should be increased exercise-induced increase in LDL particle size, which is associated with reduced susceptibility to LDL oxidation (14). Regular exercise and high aerobic capacity are associated with increased activities of skeletal muscle LPL and plasma lecithin-cholesterol acyltransferase and reduced hepatic lipase activity (26, 40, 45), thereby promoting the catabolism of TG-enriched lipoproteins that are considered to be a major source of small dense LDL. Moreover, the high-fitness group tended to have lower levels of plasma OxLDL (which plays a central role in atherosclerosis and CHD) than the low-fitness group (Table 2, P = 0.059). Exercise-induced increases in blood flow and endothelial shear stress induce activation of endothelial nitric oxide synthase (38), and increased nitric oxide protects against the oxidative modification of LDL (25). Therefore, regular exercise and a sustained high level of CRF prevent atherosclerosis and CHD by improving the quality of the circulating LDL. Nevertheless, because it was reported that the risk alleles of SNPs associated with blood lipoprotein levels additively increase the risk for CHD (29, 31), individuals at high genetic risk for elevated blood LDL-C levels should be concerned with their lipid profiles even though they are physically active and maintain a high level of CRF.

The present study has several limitations. First, our sample size was relatively small, which might have led to a type 2 error. Second, because it was a cross-sectional study, the interaction effects between CRF and polygenic risk on the incidence of CHD were not examined. Ahmad et al. (1) report that the genetic risk for low HDL-C associated with the LPL rs10096633 minor allele was attenuated in physically active women, whereas the risk for myocardial infarction was higher in rs10096633 minor allele carriers than noncarriers regardless of the physical activity level. These results suggest that the effects of regular exercise and SNPs on both lipid phenotypes and the incidence of CHD differ depending on the outcomes. Prospective and interventional studies will elucidate whether the CRF level significantly influences the relationship between the polygenic risk for dyslipidemia and the incidence of CHD. Third, our study included only male subjects. Several studies report that exercise-induced changes in lipid metabolism differ by sex (10, 28). Therefore, further investigation is needed to confirm our findings in female subjects. Finally, although CRF itself is not only acquired by regular exercise but also determined by intrinsic factors such as genetic variations, we did not distinguish intrinsic or acquired CRF in the present study. Lessard et al. (35) show that in a rat model of low aerobic response to training, aerobic capacity and metabolic disease risk could not be improved despite 8 wk of endurance exercise training, whereas high responders showed lower metabolic risk. Therefore, it is possible that individuals with high CRF in the present study were intrinsically resistant to hypertriglyceridemia regardless of TG-associated SNPs. In the future, genetic association studies, including SNPs associated with trainability of aerobic capacity, are required to address this issue.

In conclusion, the present study revealed that high CRF attenuates the polygenic risk for hypertriglyceridemia but does not modify the polygenic effects on serum LDL-C and HDL-C levels in Japanese men.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: K.T., M.T., and M.H. conception and design of research; K.T., T.I., X.S., Z.-B.C., and S.S. performed experiments; K.T. and X.S. analyzed data; K.T. interpreted results of experiments; K.T. prepared experiments; K.T., T.I., X.S., S.S., M.T., and M.H. edited and revised manuscript; K.T., T.I., X.S., Z.-B.C., S.S., M.T., and M.H. approved final version of manuscript.

REFERENCES


